REMARKS

Claims 1-7, 10, and 14-30 are pending.

Amendments

The amendments to the claims are meant in part to respond to the rejection, and to accurately and clearly reflect the scope and parameters of the invention claimed herein.

The amendments to the specification are meant to correct the interpretative statements therein regarding the data reported in the tables and charts in the specification. One of ordinary skill in the art would readily recognize that the original descriptions and statements were incorrect, and would see from the data reported that the corrections made herewith are necessary and correct.

Rejection of Claims Under 35 USC § 102(a,e)

Claims 1, 3-5, 7, 14-16, 21-25, 29, and 30 were rejected under 35 USC § 102(a,e) as being anticipated by Timpe U.S. Patent No. 6,063,404 ("Timpe"). Timpe is said to teach a method of delivering a sex hormone via a bioadhesive composition to a mucosal surface, wherein the composition includes the hormone, a bioadhesive, water insoluble cross-linked polycarboxylic polymer (polycarbophil) and a water soluble polymer (carbopol). The rejection notes that "Timpe does not specifically disclose that the prior art tablet would progressively hydrate. However, since the prior art tablet is composed of the same ingredients as the instant tablet, it is inherent that the prior art tablet would also

progressively hydrate.... See abstract, column 1 lines 22-24, column 2 lines 50-65, column 3 line 3 - column 4 line 40."

Applicants respectfully disagree with the rejection. Viewed properly and in context, and as interpreted correctly by the Examiner, Timpe is nevertheless not relevant to the instant invention. The key focus is progressive hydration, and just what causes a formulation to progressively hydrate over time. The bottom line is that Timpe does not in any manner disclose, teach, or suggest a progressive hydration formulation, regardless of the particular ingredients used.

Timpe addresses bioadhesive tablets "with at least one surface of the tablet comprising concentric or parallel, straight and/or curved depressions." Col. 2, lines 52-55. The tablets "can be produced in a known way. Any active ingredient ... can be moulded into tablets that adhere to the mucosa by adding a bioadhesive adjuvant ... and optionally other adjuvants common in tableting using a simple technique." Col. 4, lines 13-18. The pharmaceutical products contemplated by Timpe "are produced in a generally known way at an appropriate dosage ... using the common solid **or liquid substrates** or diluents and adjuvants commonly used in pharmaceutical engineering." Col. 4, lines 41-45 (emphasis added).

Thus, Timpe does not contemplate a product that only progressively hydrates, and that necessarily includes both a water soluble polymer and a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer. Instead, Timpe's suggested

formulations typically are produced with liquid, and so are already hydrated to a significant degree even before administration.

(1) There is no mention, teaching, or suggestion in Timpe regarding progressive hydration, or any recognition that some treating agents may need to be, or may be, protected from direct or indirect effects of being contacted with moisture a significant time before being made bioavailable to the patient. Thus, there is not even a recognition or teaching of the particular problem addressed by the instant invention, let alone of the particular solution provided. Instead, Timpe merely relies on production "in a generally known way at an appropriate dosage ... using the common solid or liquid substrates or diluents and adjuvants commonly used in pharmaceutical engineering." Col. 4, lines 41-45.

(2) Timpe expressly focuses and relies on the grooves in its tablets, and on the ability of its compositions to swell -- which relies on absorption of moisture -- for the purpose and intent disclosed and described therein. See, e.g., col. 2, lines 52-56; col. 5, lines 39-41. Timpe's formulation is merely intended to make available the active agents "for resorption across an extensive tissue area of the target organ," col. 2, lines 64-65, and to "stimulate [the active agent's] resorption by the tissue." Col. 2, line 66 to col. 3, line 2. Again, there is no disclosure, teaching, or recognition of the instant problem or solution – providing progressive hydration to enable protection of sensitive treating agents.

(3) Timpe does not recognize, disclose, or teach the advantage of having both kinds of polymers present in the formulation, as claimed here. For example, Timpe, at Example 1, contains progesterone, cyclodextrin, mannitol, and vehicle. See col. 6, lines 6-10. Further,

Timpe merely suggests that its compositions need only contain "at least one bioadhesive adjuvant." Col. 2, lines 52-54. Such an adjuvant is described in Timpe as **preferably** developing adhesion "when coming into contact with the mucosa, such as a cellulose, a cellulose derivative, a carboxyvinyl polymer, a derivative of a carboxyvinyl polymer, a lectin or natural material or mixture of said substances." Col. 3, lines 3-8 (emphasis added). Thus, Timpe does not recognize the importance of the particular bioadhesive polymer crucial to the instant invention but only incidental to certain of Timpe's formulations. Nor is there any disclosure or recognition of the advantage of the particular combination of polymers in the instant invention.

(4) Timpe does not set forth any particular method of preparing its formulations, instead referring to "known" procedures. See, e.g., col. 4, lines 13-18, and lines 41-45. Generally, most pharmaceutical tablets are not produced in a 'dry' manner, but rather, for convenience and safety, using wet methods. Further, Timpe's examples all rely on the ingredients being specifically "mixed and **moulded** into tablets in the known way." Col. 6, lines 13-14, 36-37, and 64-65; and col. 7, lines 22-23 (emphasis added). Such "molded" tablets are -- like most tablets – generally prepared using moistened ingredients, prepared to be rapidly soluble. See, e.g., Remington's The Science and Practice of Pharmacy, 20th Edition (2000), at pages 859, 881 (a copy of which is attached hereto). Thus, Timpe does not disclose or suggest preparing tablets in a 'dry' manner with regard at least to the treating agent -- which would be important to any formulation intended to progressively hydrate, thereby to protect its treating agent from the potential effects of moisture. In fact, Timpe

actually teaches away from the instant invention, mentioning only a manufacturing method that would not provide progressive hydration.

(5) As discussed in the Amendment And Response filed April 24, 2001 (at pages 7-9), and in the Response And Amendment filed October 25, 2001 (at pages 10-12), the mere presence in a formulation of the same ingredients as claimed in the instant invention does not suggest or provide a progressive hydration formulation, without specific, unusual preparation intended for that particular result. Further, even initially "dry" preparations -- which are uncommon anyway -- may and often do absorb moisture quickly (and swell), even if they don't release the treating agent all at once. In contrast, progressive hydration formulations as defined and used herein must be able to maintain 'dryness' for much of the treating agent for an extended period of time.

Thus, Timpe cannot be reasonably interpreted to disclose, teach, or suggest the instant invention: use of both a water soluble polymer and a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer, in a formulation that is prepared in a manner that provides progressive hydration upon application to a patient. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection of Claims Under 35 USC § 103(a)

Claims 1-7, 10, and 14-30 are rejected under 35 USC § 103(a) as being unpatentable over Timpe, as cited above. The rejection notes that "Timpe does not teach the instant amount range of said hormone. However, one having ordinary skill in the art would have been expected to determine the optimum amounts through routine

experimentation. One would have been motivated to do this in order to develop a method/composition that would deliver the optimum amount of said hormone to the mucosal surface."

Applicants respectfully disagree. The particular dosing of the hormone is not the key issue here. As discussed in detail above, Timpe simply does not in any manner teach, disclose, teach, recognize, or suggest the instant invention: (1) use of both a water soluble polymer and a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer, (2) prepared to produce a progressive hydration formulation. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

In light of the above remarks, Applicants respectfully request reconsideration and withdrawal of the rejections, and Applicants respectfully solicit a Notice of Allowance. If it would be convenient to the Examiner, the applicants' patent attorney may be reached directly at the Washington, D.C. telephone number provided below.

Respectfully submitted,

LYON & LYON LLP

Dated: March 6, 2002 By: _____

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20 TH EDITION

Remington: The Science and Practice of Pharmacy

ALFONSO R GENNARO
Chairman of the Editorial Board
and Editor

Figure 45-1. Tablet press operators checking batch record in conformance with Current Good Manufacturing Practices (courtesy, Lilly).

three layers. Special tablet presses are required to make layered tablets such as the Versa press (*Stokes/Pennwalt*).

Press-Coated Tablets—Such tablets, also referred to as dry-coated, are prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets. They have all the advantages of compressed tablets, ie, slotting, monogramming, speed of disintegration, etc, while retaining the attributes of sugar-coated tablets in masking the taste of the drug substance in the core tablets. An example of a press-coated tablet press is the *Manesty* Drycota. Press-coated tablets also can be used to separate incompatible drug substances; in addition, they can provide a means of giving an enteric coating to the core tablets. Both types of multiple-compressed tablets have been used widely in the design of prolonged-action dosage forms.

Controlled-Release Tablets—Compressed tablets can be formulated to release the drug slowly over a prolonged period of time. Hence, these dosage forms have been referred to as *prolonged-release* or *sustained-release* dosage forms as well. These tablets (as well as capsule versions) can be categorized into three types: (1) those that respond to some physiological condition to release the drug, such as enteric coatings; (2) those that release the drug in a relatively steady, controlled manner; and (3) those that combine combinations of mechanisms to release *pulses* of drug, such as repeat-action tablets. The performance of these systems is described in more detail in Chapter 47.

Tablets for Solution—Compressed tablets to be used for preparing solutions or imparting given characteristics to solutions must be labeled to indicate that they are not to be swallowed. Examples of these tablets are Halazone Tablets for Solution and Potassium Permanganate Tablets for Solution.

Effervescent Tablets—In addition to the drug substance, these contain sodium bicarbonate and an organic acid such as tartaric or citric. In the presence of water, these additives react, liberating carbon dioxide that acts as a distintegrator and produces effervescence. Except for small quantities of lubricants present, effervescent tablets are soluble.

Compressed Suppositories or Inserts—Occasionally, vaginal suppositories, such as Metronidazole Tablets, are prepared by compression. Tablets for this use usually contain lactose as the diluent. In this case, as well as for any tablet intended for administration other than by swallowing, the label must indicate the manner in which it is to be used.

Buccal and Sublingual Tablets—These are small, flat, oval tablets. Tablets intended for buccal administration by inserting into the buccal pouch may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure to give a hard tablet. Progesterone Tablets may be administered in this way.

Some newer approaches use tablets that melt at body temperatures. The matrix of the tablet is solidified while the drug is in solution. After melting, the drug is automatically in solution and available for absorption, thus eliminating dissolution as a rate-limiting step in the absorption of poorly soluble compounds. Sublingual tablets, such as those containing nitroglycerin, isoproterenol hydrochloride, or erythrityl tetranitrate, are placed under the tongue. Sublingual tablets dissolve rapidly, and the drug substances are absorbed readily by this form of administration.

MOLDED TABLETS OR TABLET TRITURATES (TT)

Tablet triturates usually are made from moist material, using a triturate mold that gives them the shape of cut sections of a cylinder. Such tablets must be completely and rapidly soluble. The problem arising from compression of these tablets is the failure to find a lubricant that is completely water-soluble.

Dispensing Tablets (DT)—These tablets provide a convenient quantity of potent drug that can be incorporated readily into powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.

Hypodermic Tablets (HT)—Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. Since stable parenteral solutions are now available for most drug substances, there is no justification for the use of hypodermic tablets for injection. Their use in this manner should be discouraged, since the resulting solutions are not sterile. Large quantities of these tablets continue to be made, but for oral administration. No hypodermic tablets ever have been recognized by the official compendia.

For medicinal substances, with or without diluents, to be made into solid dosage forms with pressure, using available equipment, it is necessary that the material, either in crystalline or powdered form, possess a number of physical characteristics. These characteristics include the ability to flow freely, cohesiveness, and lubrication. The ingredients such as disintegrants designed to break the tablet up in gastrointestinal (GI) fluids and controlled-release polymers designed to slow drug release ideally should possess these characteristics or not interfere with the desirable performance traits of the other excipients. Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material that is to be compressed into tablets.

The basic mechanical unit in all tablet-compression equipment includes a lower punch that fits into a die from the bottom and an upper punch, with a head of the same shape and dimensions, which enters the die cavity from the top after the tableting material fills the die cavity (see Fig 45-2). The tablet is formed by pressure applied on the punches and subsequently is ejected from the die. The weight of the tablet is determined by the volume of the material that fills the die cavity. Therefore, the ability of the granulation to flow freely into the die is important in ensuring a uniform fill, as well as the continuous movement of the granulation from the source of supply or feed hopper. If the tablet granulation does not possess cohesive properties, the tablet after compression will crumble and fall apart on handling. As the punches must move freely within the die and the tablet must be ejected readily from the punch faces, the material must have a degree of lubrication to minimize friction and allow the removal of the compressed tablets.

There are three general methods of tablet preparation: the wet-granulation method, the dry-granulation method, and direct compression. The method of preparation and the added ingredients are selected to give the tablet formulation the desirable physical characteristics allowing the rapid compression of tablets. After compression, the tab-

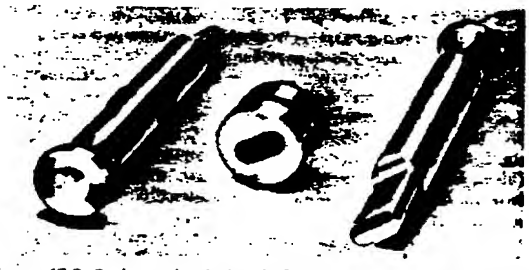

Figure 45-2. Basic mechanical unit for tablet compression: lower punch, die, and upper punch (courtesy, Vector/Colton).

Tablet triturates are small, discoid masses of molded powders weighing 30 to 250 mg each. The base consists of lactose, d-lactose, mannitol, dextrose, or other rapidly soluble materials. It is desirable in making tablet triturates to prepare a solid dosage form that is rapidly soluble; as a result they are generally softer than compressed tablets.

This type of dosage form is selected for a number of drugs because of its rapidly dissolving characteristic. Nitroglycerin in many concentrations is prepared in tablet triturate form since the molded tablet rapidly dissolves when administered by placing under the tongue. Potent alkaloids and highly toxic drugs used in small doses are prepared as tablet triturates that can serve as dispensing tablets to be used as the source of the drug in compounding other formulations or solutions. Narcotics in the form of hypodermic tablets originally were made as tablet triturates because they rapidly dissolve in sterile water for injection prior to administration. Today with stable injections of narcotics available, there is no longer any justification for their use in this manner. Although many hypodermic tablets currently are made, they are used primarily for oral administration.

Tablet triturates are made by forcing a moistened blend of the drug and diluent into a mold, extruding the formed mass, which is allowed to dry. This method is essentially the same as it was when introduced by Fuller in 1878. Hand molds may vary in size, but the method of operation is essentially the same. Molds consist of two plates made from polystyrene plastic, hard rubber, nickel-plated brass, or stainless steel. The mold plate contains 50 to 500 carefully polished perforations. The other plate is fitted with a corresponding number of projecting pegs or punches that fit the perforations in the mold plate. The mold plate is placed on a flat surface, the moistened mass is forced into the perforations, and the excess is scraped from the top surface. The mold plate is placed over the plate with the corresponding pegs and lowered. As the plates come together, the pegs force the tablet triturates from the molds. They remain on the tops of the pegs until dry, and they can be handled (see Fig 45-33). In some hand molds, as shown in Figure 45-34, the pegs are forced down onto the plate holding the moist trituration.

FORMULATION

In developing a formula it is essential to know the blank weight of the mold that is to be used. To determine this, the weight of the diluent that exactly fills all the openings in the mold is determined by experiment. This amount of diluent is weighed and placed aside. The total amount of the drug required is determined by multiplying the number of perforations in the plate used in the previous experiment by the amount of drug desired in each tablet. The comparative bulk of this medication is compared with that of an equal volume of diluent and that quantity of diluent is removed and weighed. The drug and the remaining diluent are mixed by trituration, and the resulting triturate is moistened and forced into the openings of the mold. If the perforations are not filled completely, more diluent is added, its weight noted, and the formula written from the results of the experiments.

It is also permissible in the development of the formula to weigh the quantity of medication needed for the number of tablets represented by the number of perforations in the mold, triturate with a weighed portion (more than ½) of the diluent, moisten the mixture, and press it into the perforations of the mold. An additional quantity of the diluent is moistened immediately and also forced into the perforations in the plate until they are filled completely. All excess diluent is removed, the trial tablets are forced from the mold, then triturated until uniform, moistened again, if necessary, and remolded. When these tablets are dried thoroughly and weighed, the difference between their total weight and the weight of medication taken will indicate the amount of diluent required and accordingly supply the formula for future use for that particular tablet triturate.

For proper mixing procedures of the medication with the diluent see Chapter 37.

Figure 45-33. Hand-molding tablet triturates (courtesy, Merck).

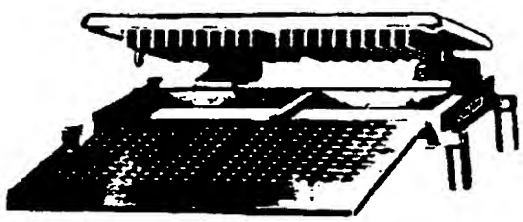

Figure 45-34. Tablet triturate mold (courtesy, Vector/Colton).

PREPARATION

The mixed powders are moistened with a proper mixture of alcohol and water, although other solvents or moistening agents such as acetone, petroleum benzin, and various combinations of these may be used in specific cases; the agent of choice depends on the solvent action that it will exert on the powder mixture. Often the moistening agent is 50% alcohol, but this concentration may be increased or decreased depending on the constituents of the formula. Care must be used in adding the solvent mixture to the powder. If too much is used, the mass will be soggy and will require a long time to dry, and the finished tablet will be hard and slowly soluble; if the mass is too wet, shrinkage will occur in the molded tablets; finally, a condition known as creeping will be noticed. Creeping is the concentration of the medication on the surface of the tablet caused by capillarity and rapid evaporation of the solvent from the surface. Because molded tablets by their very nature are quite friable, an inaccurate strength in each tablet may result from creeping if powder is lost from the tablet's surface. On the other hand, if an insufficient amount of moistening agent is used, the mass will not have the proper cohesion to make a firm tablet. The correct amount of moistening agent can be determined initially only by experiment.

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Notes/Comments:

Please submit the attached RESPONSE AND AMENDMENT for the following application:

In re Application of:	)	Group Art Unit: 1616
William J. BOLOGNA, et al.	)	
Serial No.: 09/596,073	)	Examiner: Alton N. Pryor
Filed: June 16, 2000	)	
For: BIOADHESIVE PROGRESSIVE HYDRATION TABLETS	)	

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